Abstract of Thesis

Name (NAG PRIYANKA)	
Title	Epithelial specific *Tmem2* plays an essential role in amelogenesis (上皮特異的TMEM2はエナメル質形成に必要である)

Abstract of Thesis

[Introduction] Developmental defects of tooth are the most common anomalies occurs in the craniofacial region. The complex interaction between genetic and environmental factors affects the enamel structure, size, shape and eruption of tooth. Hyaluronic acid, the main component of extracellular matrix, act as a key element in the periodontal tissue and contributes their structural and physiological functions. Earlier studies revealed the gene expression pattern of hyaluronan synthase (HAS) indicating that three HAS isotopes are prenatal and postnatal factor for HA synthesis in tooth germ, involved in mouse molar morphogenesis and cytodifferentiation, also regulate crown and root formation of tooth germ. *Tmem2* (Transmembrane protein 2) is the novel cell surface hyaluronidase. Previous evident suggested that deficiency of *Tmem2* during embryogenesis develop craniofacial and cardiac malformation which indicated that *Tmem2* is critical for embryogenesis.

[Objectives] The novel degrading enzyme *Tmem2* is critical for HA function. Tooth development is an excellent model to investigate the cellular dynamics in ectodermal derived organs. Therefore,

The objective of this study is to investigate the significance of *Tmem2* during enamel development of tooth.

[Methods] The expression of *Tmem2* in amelogenesis was analyzed by *in situ* hybridization at their postnatal day (P)14. *Tmem2* ablation targeted to dental epithelium were generated by crossing the *Tmem2*^{flox} allele and the *K14-Cre* transgene. Morphological assessment was performed by micro-CT analysis at three different chronological lifetime 6-months, p28 and p14 both control and K-14Cre;*Tmem2*$^{flox/flox}$ *(Tmem2-CKO)* mice. For histological analysis, paraffin and frozen sections were used for haematoxyline & eosin and immunohistochemical staining.

[Results] *Tmem2* expressed pre-secretory (PAB), secretory (SAB) and maturation (MAB) of ameloblast. Morphological assessment indicated significant reduction in enamel layer and altered enamel prism structure in *Tmem2* deficient mice at p14. *Tmem2* deficient mice show severe attrition of enamel at the age of p28 and 6-months. Histological evaluation done by H&E staining suggested loose cell-basement membrane, cell-cell attachment present in PAB, SAB & MAB layer in *Tmem2-CKO* mice. Moreover, *Tmem2* deficiency results abnormal accumulation of HA on the cell surface and impaired focal adhesion formation. Abnormal accumulation of HA disrupted the junctional complexes of epithelium leads loss of cell polarity and cell-cell adhesion during matrix protein secretion in *Tmem2* deficient mice.

[Conclusion] The evidence indicated *Tmem2* deficient mice develop amelogenesis imperfecta. Hence, the novel cell surface hyaluronidase *Tmem2* crucial for enamel development.

様式７

論文審査の結果の要旨及び担当者

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論文審査の結果の要旨

本研究は、遺伝子改変動物を用いてヒアルロン酸分解酵素 Transmembrane protein 2 (TMEM2)のエナメル質形成における役割について検討したものである。

その結果、TMEM2 はエナメル芽細胞の細胞接着に関与しており、エナメル質形成において正常な量や質を獲得するうえで必須であることを見出した。

これらの成果は、エナメル質形成における新たな制御機構の一端を明らかにし、エナメル質形成不全症などの歯の形成異常の原因解明につながる重要な知見を与えるものであり、博士（歯学）の学位論文として価値のあるものと認める。